1-VINYLPYRROLIDIN-2-ONE/ ESTER COPOLYMERS

Field of the invention

The present invention relates to 1-vinylpyrrolidin-2-one/ ester copolymers.

Background of the invention

Controlled release drug systems based on biodegradable polymers, in the form of thin layers, needles, micro- and nanospheres, are acquiring ever greater importance due to their ease of use and elimination of the problem of their explantation after the drug has depleted. In this respect, the matrices can be programmed to break down after a certain time into bioeliminable and non-toxic products, with consequent complete elimination from the body via normal excretion paths.

This technique is used principally for peptides and proteins with potentially great therapeutic usefulness, but if administered as such would have an extremely brief average lifespan within the body, thus prejudicing their applicability in practise.

Among these proteic drugs there are many however which give or would give excellent results if inserted in controlled release systems, thus ensuring their release into the organism with controlled kinetics such as to even out their elimination rate, hence maintaining them at an optimum concentration in biological fluids for long periods.

The biodegradable polymers which comprise the most frequently used controlled release systems are polyester based, among which of particular importance are copolymers of glycolic acid and lactic acid, currently known as PLGA. Less frequently considered are polyesters different from PLGA, polycarbonates, polyanhydrides, polyorthoesters etc.

One problem which frequently presents itself in biodegradable controlled release systems which incorporate proteic drugs is the poor affinity of these latter for the matrix in which they are incorporated, with which they have scant or no chemical or physical interactions. This entails on the one hand difficulty with homogenous dispersion in the matrix, and on the other hand serious irregularities in release kinetics. In particular, a phenomenon known as "out-burst" can occur, consisting of the virtually immediate release of a part of the drug after insertion into the body of the biodegradable device containing it.

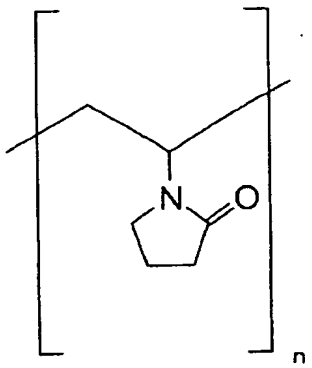
Out-burst is damaging in two ways. On the one hand, a substantial part of the drug is lost in order to maintain an optimum therapeutic level over time, because by detaching rapidly it is also rapidly eliminated. On the other hand, rapid intake of relatively substantial levels of the drug into the body can lead to undesirable side effects.

The out-burst phenomenon is due to the fact that part of the drug, not being very compatible (i.e. miscible) with the matrix, accumulates near its surface instead of dispersing uniformly within the device, and hence detaches rapidly therefrom.

It appears evident that an objective need exists to study new biodegradable matrices which, on degrading, transform into bioeliminable and definitely non-toxic products while at the same time having a greater affinity with peptidic or proteic drugs.

The ability of poly-N-vinylpyrrolidinone, or polyvinylpyrrolidone as it is commonly known, hereinafter abbreviated to PVP, to complex with many substances and its non-toxicity are well known. Due to its properties, this polymer is widely used as an ingredient in many food and pharmaceutical applications, for external or oral use.

This polymer is in particular characterized by having the following formula:

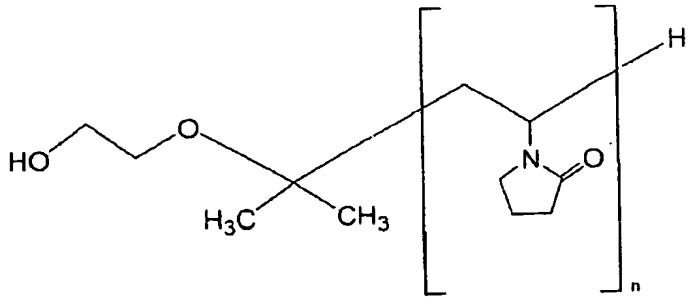


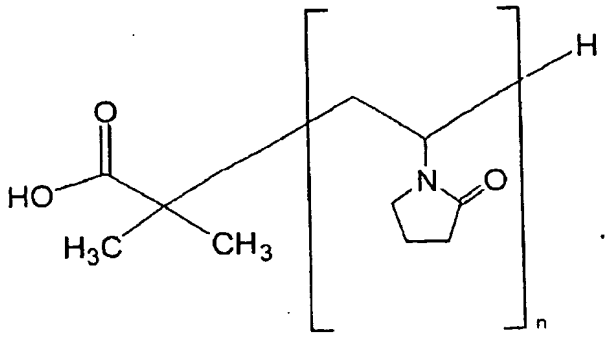
In the past, high molecular weight PVP was widely used in medicine also for systemic use, in particular (in aqueous solution) as a plasma substitute.

This use, however, and all internal uses of high molecular weight PVP, were terminated because it was discovered that this polymer is not biodegradable, and if of high molecular weight, i.e. above the threshold of renal filtration (which for PVP is around a molecular weight of 40,000) it is no longer eliminated and remains in the body indefinitely, where however it has never given rise to toxic effects of any kind.

Recently however synthesis methods have been established to obtain oligomeric PVPs of molecular weights between 1,000 and 10,000, well below the renal elimination threshold, and bearing at one end a carboxyl (also in the form of a methyl or ethyl ester), or hydroxyl function (F. M. Veronese, L. Sartore, P. Caliceti, O. Schiavon, E. Ranucci, P. Ferruti, *J. Bioact. Compat. Polym.* 1990, 5, 167; P.Caliceti, O. Schiavon, F.M. Veronese, L. Sartore, E. Ranucci, R. Ferruti, *J. Bioact. Compat. Polym.* 1995, 10, 103; E. Ranucci, G. Spagnoli, F. Bignotti, L. Sartore, P. Ferruti, P. Caliceti, O. Schiavon, F.M. Veronese, Macromol. *Chem. Phys.*, 1995, 196, 763).

These copolymers are in particular characterised by having the following formulas:





In addition, a lactone function has also been inserted using the same technique (M. Tarabic, E. Ranucci, *Macromol. Biosci.* 2001, 1, 126).

Summary of the invention

An aspect of the present patent application consists of biodegradable and completely bioeliminable polymer products in the form of polyesters modified by the introduction of short PVP chains, which ensure their high affinity with a number of traditional or proteic drugs. More specifically it concerns polyesters to which the oligomeric PVPs are linked by means of ester bond, and therefore by definition resolvable in the body. This ensures complete biodegradability of the new materials, which, once inserted into the body are transformed over time into simple acids and alcohols and into the starting oligomeric PVPs, these being easily bioeliminable.

The invention also relates to processes for preparing the copolymers and compositions containing them.

Brief description of the figure

Figure 1 reports a schematic representation of the formula of branched or hyperbranched copolymers according to the present invention wherein the PVP segments are located at the terminal ends of the branches

Figure 2 reports a schematic representation of the branched or hyperbranched copolymers according to the present invention having PVP segments and residues derived from monocarboxylic acids or monohydroxylated alcohols.

Detailed description of the invention

The invention therefore provides segment copolymers in which segments "A" of polyvinylpyrrolidone (PVP) structure and segments "B" of polyester structure are present.

Said copolymers can assume various configurations, being present for example in the form of linear copolymers in two blocks, of A-B type, with structure of the type:

$PVP\text{-}COO\text{-}(R^3\text{-}COO)_nH$,

where n is a number between 5 and 500, preferably between 15 and 150, and R^3 is a linear or branched hydrocarbon chain containing from 1 to 12 carbon atoms, preferably from 1 to 6 carbon atoms;

or with structure of the type

$PVP\text{-}(OOC\text{-}R^3)_nOH$,

where n is a number between 5 and 500, preferably between 15 and 150, and R^3 is a linear or branched hydrocarbon chain containing from 1 to 12 carbon atoms, preferably from 1 to 6 carbon atoms.

Alternatively, the copolymers of the invention can be of the linear type in three blocks, of A-B-A type, in particular of formula:

$PVP\text{-}COO\text{-}(R^1\text{-}OOCR^2COO)_n\text{-}R^1\text{-}OOC\text{-}PVP$,

where n is a number between 5 and 300, preferably between 10 and 100, and R^1 and R^2, equal or different, are linear or branched hydrocarbon chains containing from 1 to 25 carbon atoms, preferably from 1 to 8 carbon atoms;

or of formula:

$PVP\text{-}(OOC\text{-}R^1\text{-}COOR^2)_nOOCR^1COO\text{-}PVP$,

where n is a number between 5 and 300, preferably between 10 and 100, and R^1 and R^2 are as aforedescribed.

Again, the copolymers of the invention can be branched or hyper-branched, with the PVP segments located at the terminal ends of the branches. A schematic and explanatory illustration of this type of copolymer is given in Figure 1, wherein A is polyvinylpyrrolidone, D is the residue deriving from a polycarboxylic or polyol, wherein the hydroxy or carboxy functions are at least 3, (BC) indicate the repeating unit of the B polyester segment and n is comprised between 2 and 200

At the ends of the branches can be located either PVP segments or residues derived from monocarboxylic acids R-COOH or monohydroxylated alcohols of the

R-OH type where R is a linear or branched hydrocarbon chain containing from 1 to 25 carbon atoms, preferably from 1 to 8 atoms. A schematic and explanatory illustration of this type of copolymer is given in Figure 2, wherein A indicates the polyvinylpyrrolidone chains, D is the residue deriving from a polycarboxylic or polyol, said hydroxylic or carboxylic functions being at least 3, (BC) indicate the repeating unit of the B polyester segment n is comprised between 2 and 200, and E is the residue of a monofunctional alcohol.

Alternatively, at the ends of the branches can be located either PVP segments or residues derived from dicarboxylic acids HOOC-R-COOH or dihydroxylic alcohols of the HO-R-OH type where R is a linear or branched hydrocarbon chain as aforedefined.

The branching sites consist preferably of polyol or polycarboxylic acid residues having a number of functions (hydroxyl or carboxyl respectively) between 3 and 12, preferably between 3 and 6.

The molar ratio between the number of branching sites and polyester fragments is a number between 0.01 and 2, preferably between 0.1 and 1.5 while the molar ratio between the number of branching sites and PVP fragments is a number between 0.01 and 100, preferably between 0.1 and 10.

If desired, the copolymers of the invention, whether branched or hyper-branched, can be cross-linked by forming a certain number of connections between chains, thus rendering them insoluble and infusible.

Finally the copolymers can present the PVP segments comb-grafted at one end onto the polyester chains.

The copolymers of the invention have preferably their PVP segments of molecular weight between 600 and 15,000, preferably between 1,000 and 6,000 and a PVP content by weight of between 5% and 95%, preferably between 10% and 50%.

The average molecular weight of the copolymers is between 10,000 and 1,000,000, preferably between 20,000 and 200,000.

The copolymers of the invention can be prepared by known methods. For example, with hydroxylated or carboxylated PVP the preparation process consists of modifying a classical multifunctional polycondensation process by introducing into the monomer mixture monofunctional compounds, and, in particular, PVP

oligomers functionalised at one end, as aforedescribed.

The theoretical considerations which form the basis of the process are given in the following paragraphs.

In all polycondensations which involve monomers with complementary functions of type "*a*" and "*b*", for example diacids and diols, two parameters can be defined which govern the progress thereof. One of these is the initial stoichiometric ratio between the two types of functions, indicated by "*r*", in which by convention the deficiency functions are named "*a*" and are placed as numerator:

$r=Na_0/Nb_0$

where the subscript "$_0$" indicates that it concerns the initial conditions. It is evident that r is by definition ≤ 1.

The other parameter is the extent of reaction, indicated by "*p*" which is calculated on the deficiency functions and defined as:

$p=Na_0-Na/Na_0$

where Na indicates the number of functions of type "*a*" present at the moment of observation. The parameter p is therefore also by definition ≤ 1.

It can be noted that a polycondensation that totally or partially involves monomers with functionality greater than 2 (multi- or polyfunctional polycondensation) can give rise, above a certain p value, known as the "critical extent of reaction" and indicated as "p_c", to cross-linked and insoluble products. Above this extent of reaction the system loses its mobility and thus p_c is also called "gelation point".

The critical extent of reaction p_c, which corresponds to the gelation point, is given by the Flory and Stockmayer formula:

$$p_c = \frac{1}{\left\{r\left[1+\rho(f-2)\right]\right\}^{\frac{1}{2}}}$$

(1)

where ρ is the fraction of functions "a" belonging to the monomer with functionality > 2 (known as a^f) over the total functions of the same type (known as a_0):

$$\rho = \frac{a^f}{a_0}$$

(2)

and r, as before, is the initial stoichiometric ratio, calculated as usual by placing as numerator the lesser function, whether or not it contains a multifunctional quota.

It is apparent that in (1) p (and therefore also p_c) and r are in mutual correspondence. In particular, a critical stoichiometric ratio r_c will exist above which the system can gel, but below which the system is unable to gel. At values of $r < r_c$ whatever the value of p, a branched but not cross-linked polymer is obtained which is therefore as a rule fusible and soluble in suitable solvents.

The value of r_c is obtained logically by putting p_c equal to 1. In this respect, by definition it is not given that p (and therefore also p_c) exceeds the value of 1. By therefore putting p =1 and solving (1) for r:

$$r_c = \frac{1}{1+\rho(f_A-2)}$$

(3)

and, if ρ=1, i.e. if the polyfunctional monomer is the only one with that type of function, equation (3) reduces to:

$$r_c = \frac{1}{f-1} \qquad (4)$$

It is to be recognised that (1) does not apply where monofunctional compounds are present. For these systems an alternative formula has been elaborated which is also valid where monofunctional compounds are present.

$$p_c = \frac{1}{\left[r(f_{w.A}-1)(f_{w.B}-1)\right]^{1/2}}$$

where $f_{w.A}$ and $f_{w.B}$ are the "weight" averages of the functionalities of the monomers present, including monofunctionals, defined thus:

$$f_{w.A} = \frac{\sum f_{A,j}^2 N_{A,j}}{\sum f_{A,j} N_{A,j}} ; \quad f_{w.B} = \frac{\sum f_{B,j}^2 N_{B,j}}{\sum f_{B,j} N_{B,j}}$$

where "$f_{A,j}$" and "$f_{B,j}$" represent respectively the functionality of each monomer of type "A" and type "B", and $N_{A,j}$ and $N_{B,j}$ their respective number of moles in the system (see for example: G. Odian "Principles of Polymerization" 3rd Ed, John Wiley & Sons, USA, 1991)

In this case, again, a critical ratio r_c can be defined above which the system gels, but below which the system is unable to gel. This can be determined by putting p_c equal to 1. Thus:

$$r_c = \frac{1}{(f_{w.A}-1)(f_{w.B}-1)} \qquad (6)$$

An aspect of the present invention is the synthesis, starting from monofunctionalised PVP oligomers, of polycondensates modified with PVP which, even at the maximum extent of reaction, are, according to convenience, either hyper-branched, but not cross-linked and therefore still fusible and soluble, or more or less cross-linked.

This result is obtained by suitably measuring the reagents so that the value of r is

respectively lower or higher than r_c as defined in equation (6), using for this purpose the addition of monofunctional compounds (among which are necessarily, but not exclusively, PVP oligomers functionalised at one end) to polyfunctional polycondensation systems (for example, but not exclusively, polyfunctional polyesterifications).

In these systems, for the purposes of the present invention, oligomeric PVPs functionalised at one end with a hydroxyl or carboxyl group (also in the form of a methyl or ethyl ester) are used as monofunctional comonomers (macromonomers), diols or dicarboxylic acids are used as bifunctional comonomers, and polyols or polycarboxylic acids are used as multifunctional comonomers.

This technique allows products to be obtained with the character of polyester-PVP block copolymers with hyper-branched molecular architecture, whereby segments of polyvinylpyrrolidone structure are located at the ends of branches, in effect "closing" them.

It is therefore possible, starting from PVP oligomers monofunctionalised at one end, to obtain copolymers in which many PVP segments are present per molecule, while from the same oligomers, in a conventional linear polycondensation involving diols and dicarboxylic acids, only two PVP segments per polymer chain could be introduced.

By introducing monoacids and monoalcohols as comonomers next to the monofunctionalised PVP oligomers, some of the branches will be terminated by residues thereof, and some by PVP segments. This signifies that the weight quantity of PVP of the products can be varied within wide limits.

With this technique, very high molecular weight products can be easily obtained, while still soluble and fusible. This is achieved provided that the initial molar ratio between monomers approaches the critical ratio r_c without exceeding it.

Alternatively, cross-linked products which are insoluble but still swellable in water by virtue of their PVP content can be obtained provided that the initial molar ratio between the monomers exceeds the critical ratio r_c.

In particular the aforementioned branched or hyperbranched copolymers having the PVP segments located at the terminal ends of the branches, are prepared

effecting polycondensation of the mixtures in variable proportions of:

a) PVPs monofunctionalized at one end with hydroxyl or carboxyl groups optionally in the form of methyl or ethyl esters;

b) dicarboxylic acids and diols;

c) polyols or polycarboxylic acids having at least 3 hydroxyl or carboxyl functions,

provided that:

i) when said copolymers are not crosslinked

"r" is < r_c

ii) when said copolymers are crosslinked

"r" is > r_c

In particular the branched or hyperbranched copolymers having located at the ends of the branches PVP segments and residues derived from monocarboxylic acids R-COOH, or monohydroxylated alcohols of the R-OH type where R is a linear or branched hydrocarbon chain containing from 1 to 25 carbon atoms, are prepared with a process which comprises effecting a a polycondensation of mixtures in various proportions of:

a) PVPs monofunctionalized at one end with hydroxyl or carboxyl groups optionally in the form of methyl or ethyl esters;

b) dicarboxylic acids and diols;

c) polyols or polycarboxylic acids having at least 3 hydroxyl or carboxylic functions

d) monocarboxylic acids of type R-COOH or monohydroxylated alcohols of type ROH, where R has the aforementioned meanings,

provided that:

i) when said copolymers are not crosslinked

"r" is < r_c

ii) when said copolymers are crosslinked

"r" is > r_c.

Preferably in the aforementioned processes:

- the diols and the diacids are of respectively general formula HOOC-R^1-COOH and HO-R^2-OH, where R^1 and R^2, equal or different, are linear or branched hydrocarbon chains containing from 1 to 25 more

preferably from 1 to 8 carbon atoms;

- the polyols or polycarboxylic acids have respectively per molecule between 3 and 12, preferably between 3 an d 6 hydroxyl or carboxyl functions.

It is also possible to proceed in the opposite direction, by progressively reducing the ρ ratio to obtain products which are ever less branched.

If polyfunctional monomers are not introduced into the reaction mixture, $\rho = 0$. This signifies the presence of bifunctional polycondensation, and that the polymers obtained do not bear branches and are hence linear. Introducing into the monomer mixture some monofunctionalized PVP oligomers, these will constitute chain terminals, and two-segment linear copolymers of A-B type will be obtained, of which one (A) has PVP character and the other (B) has polyester character, or three-segment linear copolymers of ABA type, with the PVP segments located at the two ends.

In particular the copolymers of A-B type according to the present invention are prepared with a process comprising effecting a polycondensation reaction on PVP terminated at one end with a hydroxy or carboxy function with respectively :

- a biacid or a bialcohol in the presence of a monoalcohol or a monocarboxylic acid or in alternative
- a hydroxy carboxylic acid or optionally a cyclic derivative thereof,

with the proviso that ratio of total moles of OH function /total moles of COOH functions is =1.

For example, to prepare copolymers of formula

PVP-COO-$(R^3$-COO$)_n$H

or of formula

PVP-(OOC-$R^3)_n$OH,

polycondensation is undertaken between PVPs monofunctionalized at one end with hydroxyl or carboxyl groups (also in the form of methyl or ethyl esters) and hydroxycarboxylic acids of type

HO-R^3-COOH

where R^3 is a linear or branched hydrocarbon chain with carbon atoms numbering between 1 and 12, preferably between 1 and 6.

Alternatively, ring-opening polymerisation is effected, initiated by PVP

monofunctionalised at one end with hydroxyl or carboxyl groups (also in the form of methyl or ethyl esters) and involving cyclic derivatives, such as lactones, glycolides or lactides, of the hydroxyacids HO-R^3-COOH.

In particular the copolymers of ABA type are prepared with a process comprising effecting a polycondensation reaction on PVP terminated at one end with a hydroxyl or carboxyl function with a biacid or a bialcohol with the proviso that the ratio of total moles of OH function/total moles of COOH functions is =1.

For example for preparing the copolymers wherein the structure is of the type PVP-COO-(R^1-OOCR^2COO)$_n$-R^1-OOC-PVP,

or of the type:

PVP-(OOC-R^1-COOR^2)$_n$OOCR^1COO-PVP

where n is a number between 5 and 300, preferably between 10 and 100, and R^1 and R^2 can be equal or different, and are linear or branched hydrocarbon chains having from 1 to 25, preferably from 1 to 8 carbon atoms,said polycondensation reaction is carried out on PVPs monofunctionalized at one end with hydroxyl or carboxyl groups optionally in the form of methyl or ethyl esters, and mixtures of dicarboxylic acids and diols of respectively general formula HOOC-R^1-COOH and HO-R^2-OH where R^1 and R^2 have the aforementioned meanings.

With PVP containing a lactone function at one end, the preparation process consists of modifying a classic ring-opening lactone polymerisation process, using PVPs thus functionalised as macromonomers, alone or mixed with other lactones. With this method "comb" copolymers are obtained, in which the PVP chains protrude from a linear polyester chain, and the resultant product can be soluble or insoluble in water depending on PVP contents. This type of process is illustrated in example 2, wherein the ring opening polimeryzation is carried out on PVP terminating with γ-butyrolactone, in the presence of γ-butyrolactone.

The Applicant has now found a new process for preparing the comb grafted copolymers according to the present invention , said process allowing to insert the PVP segments in an already formed polyester chain , in particular PLGA commercially available.

This process is decidedly more economical than the previous one, since it allows to obtain the desired copolymer by carrying out only a polymerisation reaction.

Said process comprises effecting a chain transfer polymerisation with N-vinyl-pyrrolidone wherein in this case the chain transfer agent is the same PLGA.

In addition the Applicant has unexpectedly found that with this process it is possible to insert many polyvinylpyrrolidone chains with an average molecular weight lower than 10,000.

Such an excellent result is achieved by carrying out the aforementioned polymerisation reaction in the presence of a second transfer agent such as methylisobutyrate.

The present invention relates to the composition containing the segment copolymers according to the present invention in combination with therapeutically or cosmetically active ingredient or in alternative with dietary supplements.

The following examples are reported for illustrative but not limitative purposes

EXAMPLES

Example 1

Preparation of a polycondensate based on PVP of average numerical molecular weight 3500, succinic acid, glycerol and 1,6-hexanediol

1.1 Synthesis of a polyvinylpyrrolidone oligomer terminating at one end with a carboxyl group, hereinafter named PVP 2 COOH

Starting materials:

The starting materials used, and their respective quantities, are given in Table 1.

Table 1

Starting materials used for the synthesis of a carboxylated PVP oligomer.

N-vinylpyrrolidone (VP)	26 ml
Methyl propionate	1000 ml
Azodiisobutyronitrile (AIBN)	810.3 mg
2,6-di-*t*-butyl paracresol	803 mg

Procedure

a) Preparation of carboxylated PVP methyl ester (PVP 2 COOMe)

The methyl propionate and the VP are introduced into a 2 litre one-neck flask equipped with tap and magnetic stirrer, then de-aerated with 4 vacuum/N_2 cycles.

The AIBN is added under nitrogen flow and the temperature is thermostatically maintained at 70°C. The reaction is conducted under these conditions for 18 hours.

The heat source is removed and the *t*-butyl paracresol is added while hot and the reaction flask is left to cool to ambient temperature.

To recover the polymer, the reaction mixture volume is reduced to about 200 ml by Rotavapor then precipitated in 600 ml of cold ether under magnetic agitation. It is filtered through a Buckner funnel, dissolved in 100 ml of methylene chloride and re-precipitated under magnetic agitation in 300 ml cold Et_2O. It is filtered through a Buckner funnel and the PVP-COOMe polymer obtained is dried under nitrogen flow; the crude product is characterised by SEC (data is given in table 1).

b) Preparation of carboxylated PVP (PVP 2 COOH)

The PVP 2 COOMe polymer is dissolved in a 0.1 M aqueous sodium hydroxide solution with an excess in moles of sodium hydroxide of 5:1, and left for 16 hours under magnetic agitation. A 0.1 M HCl solution is then added until pH = 2.5.

The product is purified by Amicon ultrafiltration (3 passages through cellulose membrane with a nominal cut-off of 3000) and lyophilised. The final product is characterised by SEC (data is given in table 2)

Yield: 80.5%

Table 2

Molecular weight data obtained by SEC for PVP 2 COOMe and PVP 2 COOH.

Materials	Mn	Mw	Polydispersity index
PVP 2 COOMe	2700	6200	2.30
PVP 2 COOH	3500	6900	1.97

1.2 Preparation of the polycondensate

Starting materials:

The starting materials used, and their respective quantities, are given in Table 3.

Table 3

Starting materials and their quantities used for preparing the polycondensate

Material	Moles	grams
PVP 2 COOH	0.003	10.5
Anhydrous glycerol	0.20	18.4
Succinic anhydride	0.60	60.1
1,6-hexanediol	0.60	70.9

When all additions are complete, the system contains 1.2003 moles of COOH (it is unimportant that the carboxyls are initially mostly "masked" as anhydride), and 1.8 moles of OH, of which 0.6 moles pertain to the trifunctional (glycerol). In Stockmayer's formula, ρ=0.332 and hence r_c= 0.751. The initial stoichiometric ratio is 0.667, lower than r_c. Therefore the system will provide a hyper-branched, but not cross-linked, product.

Procedure

a) The glycerol and the PVP 2 COOH are introduced into the reactor; a small drop of 98% sulphuric acid is added and the mixture is heated to 110°C in a closed container for 5 hours. This procedure transforms the PVP 2 COOH into its glycerol ester.

b) After cooling, the succinic anhydride is added to the preceding mixture and the system is placed under slight nitrogen pressure. It is re-heated to 100°C for 2 hours then a small drop of 98% sulphuric acid is again added. This procedure transforms the products which are present (excess glycerol and PVP 2 COOH glycerol ester) into the respective hemisuccinates. At this point the hexanediol is introduced under nitrogen flow.

The system now consists of a mixture of glycerol hemisuccinate (0.197 mol), PVP 2 COOH glycerol ester disuccinate (0.003 mol) and 1,6-hexanediol (0.60 mol).

Since trans-esterification reactions actively occur as well as esterification reactions, the means of addition do not affect the calculations (see above) but prevent any losses of glycerol in the initial phase thus favouring the complete insertion of PVP 2 COOH into the polymer structure which forms.

c) After adding hexanediol, the temperature is brought to 100° C, again under slight nitrogen pressure, for 16 hours. It is now left under nitrogen flow at 100°C for 1 hour, then under vacuum (0.2 tor) at 100°C for another 4 hours. This procedure serves to eliminate the by-product (water) bringing the reaction to completion.

d) At the end, the product is removed from the reactor while still molten. By cooling over time it solidifies to a waxy solid.

The product re-swells in water, but does not dissolve. Instead, it is soluble in methanol, ethanol, chloroform and ethyl acetate. Its intrinsic viscosity in chloroform at 30°C is 0.23 dl/g.

Example 2

Preparation of a comb-copolymer, in which PVP segments of average numerical molecular weight of 3500 are grafted at one end to polyester chains.

2.1 Preparation of a PVP oligomer terminating with lactone function (PVP-γ-butyrolactone)

In a 2-neck flask, equipped with magnetic stirrer, refrigerator and a tube for nitrogen entry, N-vinyl-2-pyrrolidinone (2 g, 18.02 mmoles), γ-butyrolactone) (32 ml, 360 mmol) and AIBN (20 mg) are mixed. The solution is de-aerated via three successive evacuation cycles until a pressure of 25 m Hg is attained then nitrogen is blown in. The reaction is then maintained under nitrogen atmosphere for 24

hours at 70°C, stirring constantly. After this period, the reaction is stopped by cooling to ambient temperature and the crude product is recovered by dissolving the solid residue obtained in the minimum quantity of CH_2Cl_2 (3 ml) and then precipitating it in Et_2O. The white powdery precipitate obtained is recovered by decanting and dried by reduced pressure drying. The dried product is then dissolved in double distilled water (100 ml) and purified from monomer and lactide residues by repeated membrane ultrafiltration (AMICON) with a cut-off of 3000. The lower molecular weight fraction is discarded, while the higher molecular weight fraction (20 ml of residual solution) is recovered by lyophilising and conserved at ambient temperature. Yield: 1.8 g.

Average molecular weight determined by SEC: 3500. The transfer constant C_T is determined by using the equation:

$$C_T = \frac{\log\left(1-\frac{[M]_0}{[T]_0}\frac{\overline{Y_t}}{\overline{\overline{X_n}}}\right)}{\log\left(1-\overline{Y_t}\right)}$$

where Y_t =conversion, $[M]_0$ = monomer concentration at start time, $[T]_0$ =concentration of the transferer (i.e. D,L-lactide) at start time, and $\overline{\overline{X_n}}$ is average cumulative numerical degree of polymerisation. The value obtained is 1.7×10^{-2}.

2.2 Copolymerization of PVP-γ-butyrolactone with γ-butyrolactone by means of ring opening polymerisation.

PVP-γ (2g), γ-butyrolactone (4 g) and stannous di-octanoate (20 mg) are injected through a silicon septum into a 25 ml glass vial equipped with silcone septum, a lateral entry point connected to a tube for argon flow, a magnetic stirrer and maintained under constant argon flow. The reaction is then maintained under argon atmosphere for 24 hours at 100°C while being stirred constantly. After this period, the reaction is stopped by cooling to ambient temperature and the crude product is recovered by dissolving the semi-solid residue obtained in the minimum quantity of CH_2Cl_2 (5 ml) and then precipitating it in ET_2O. The white powdery

precipitate obtained is recovered by decanting and dried by reduced pressure drying. The precipitation of CH_2Cl_2 in Et_2O is repeated two more times. The final product appears as a white solid soluble in chlorinated solvents and re-swellable in water. Yield: 4.5 g. Average molecular weight determined by SEC: 35,000. PVP chain content : 33% (w/w).

Example 3

A PLGA sample M_n=80000 (10 g) was dissolved in VP (20 ml) while stirring at room temperature under nitrogen atmosphere. AIBN (0.01 w/w with respect to the monomer) was added to the resulting viscous solution. The reaction mixture was gently heated up to 70°C and allowed to stand at this temperature for 24 hrs under occasional stirring. After this time, it was dissolved in dichloromethane and the solid product was recovered by precipitation with four volumes ether. After drying, the crude product was extracted several times with liberal amounts of water, until no trace of un-grafted PVP was observed in the aqueous extracts. During each washing step, the product was maintained under stirring at 45°C. Yield = 12 g.

The final product was characterised by FT-IR, ^1H NMR and ^{13}C NMR spectroscopy. All spectroscopic data were in agreement with the proposed structure. Moreover, the quantitative ^1H NMR analysis indicated a PVP content equal to 27.2%.

Nitrogen content (elemental analysis)= 3.28%, in agreement with the NMR determination within the limit of the experimental error.

Apparent molecular weight (SEC): M_n= 96000, M_w= 103000.

Example 4

3.0 g of a finely powdered PLGA/PVP graft copolymer prepared according to example 1 were suspended in 100 ml 1 M NaOH aqueous solution. The suspension was stirred 7 days at room temperature. The polymer gradually dissolved. The resultant solution was acidified to pH 3 with dilute hydrochloric acid, freeze-dried, obtaining a white powder that was extracted several times with dichloromethane. The dichloromethane extracts were filtered and the total volume reduced to 50 ml by evaporation under vacuum. Finally, the addition of 250 ml of ether led to the precipitation of 0.73 g PVP, identified by IR and NMR.

SEC analysis gave the following results: M_n= 36,000, M_w= 58,000

Example 5

The same procedure as in Example 3 was followed, but with the addition of a 40 ml weight of methyl isobutyrate as additional chain transfer agent (E. Ranucci, M. Tarabić, M. Gilberti, A.-C. Albertsson, *Macromol. Chem. Phys.*, 2001, *1219*, 201). After 24 hours the reaction mixture was diluted with dichloromethane and treated as in example 1.

Nitrogen content (elemental analysis)= 2.65%, in agreement with the NMR (27% w/w) determination within the limit of the experimental error.

Apparent molecular weight (SEC): M_n= 82,000, M_w= 103,000.

Example 6

The same procedure as in Example 4 was followed, starting with the product obtained in Example 4. The PVP finally isolated (1 g) gave by SEC analysis the following results:

M_n= 3200, M_w= 7000.